REMARKS

I. Introduction

In response to the Office Action dated February 23, 2004, Applicants request reconsideration and withdrawal of the rejections for reasons discussed below. Claims 21-27 and 32-35 are pending and being examined. Claims 28-30 have been withdrawn from consideration. Applicants will postpone cancellation of non-elected claims until identification of allowable claims and in view of potential subsequent rejoinder, should circumstances permit.

Applicants appreciate the withdrawal of the rejections based on 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103(a).

II. Prior Art Rejections

At pages 2-5 of the Office Action, claims 21, 24 and 33-35 were rejected under 35 U.S.C. §102(a) as being anticipated by Sufrin et al. (U.S. Patent No. 5,652,105; hereinafter referred to as "Sufrin"), and claims 22, 23, 25-27 and 32 were rejected under 35 U.S.C. §102(a) and (e) as being anticipated by Sufrin. Applicants respectfully traverse these rejections for the following reasons.

The Examiner states, at page 4 of the Office Action, that the disclosure of Sufrin's 5-methylcytosine containing oligomeric DNA and their use of the same to inhibit mammalian DCMTase activity is seen to anticipate claims 21, 24 and 33-35. At page 5 of the Office Action, the Examiner states that the further disclosure by Sufrin of inhibiting DCMTase activity in decreasing methylation which lowers incidence of cancer is seen to anticipate claims 22-23, 25-27 and 32 of the instant application.

As stated in the previous Amendment dated November 26, 2003, prior to Applicants' invention, those skilled in the art did not know that DCMTase is regulated via an allosteric site, nor did the skilled artisan know that such allosteric inhibition could be achieved using a synthetic inhibitor molecule that comprises a C-5 methylcytosine that recognizes an allosteric site on DCMTase. Although the Examiner alleges that Sufrin discloses an oligomeric DNA analog which comprises at least one 5-methylcytosine residue which specifically interacts with DCMTase and can

be used to inhibit DNA methyltransferase activity in tumor cells, Applicants respectfully note several problems with this statement and its use as a basis for rejecting claims 21-27 and 32-35.

First, the assertion in Sufrin that their "substrates appear to interact with both an activation and a catalytic site on the enzyme" does not teach that the enzyme contains an allosteric site. An allosteric site, as is commonly understood in the art of protein chemistry and as explicitly defined in Applicants' specification at page 15, lines 10-15, is "a site other than an active site that can influence the catalytic progress of the enzyme." In contrast, an "active site is defined as the local protein environment in close proximity to the reactive substituents in the methylation reaction." Merely by positing inhibition of two distinct DNA methylation processes, *de novo* and maintenance methylation (see Sufrin at col. 7, lines 51-53) Sufrin does not teach inhibition via an allosteric site.

Even if Sufrin were construed as suggesting the possibility of an allosteric site for regulation of DCMTase activity, which Applicants do not concede, Sufrin does not present data or analysis demonstrating inhibition of DCMTase via an allosteric site. Sufrin presents data showing relative differences in enzyme activity and presumes that less activity indicates "inhibition", while more activity indicates "activation" of the enzyme. One of skill in the art of protein chemistry, however, would recognize that these results do not demonstrate whether the differences in activity can be attributed to inhibition or activation. A proper determination of enzyme inhibition requires challenging the enzyme with molecules in a battery of tests to demonstrate that a pattern of activity change consistent with inhibition is observed through rigorous numerical and graphical analysis. Such studies would also be designed to determine whether the regulatory effect observed is due to another molecule that may be present in the assay material. The data presented in Sufrin was collected using crude extracts, either whole cell or nuclear extracts. Accordingly, the DCMTase enzyme was only one of approximately 1,000 proteins present in the extract, any of which may affect DCMTase activity in a way to suggest inhibition or activation.

The studies presented in Sufrin were performed using an oligonucleotide substrate that contained 5-fluorocytosine (5FC). Sufrin attributes the inhibitory activity of its molecules to the substitution of FC for C in CG sequences (col. 5, lines 39-42). Moreoever, Sufrin did not include

studies that would determine whether the effects they observed were caused by another molecule or resulted from substrate inhibition, or to distinguish between competitive inhibition and allosteric inhibition. 5FC substrates were already understood in the art to be an active site "suicide inhibitor" well before the Sufrin application. Sufrin et al. even compare their inhibitors to the M.HhaI X-ray crystallography evidence for suicide inhibition, where the enzyme is frozen in the act of catalysis at the active site (col. 11, lines 2-5). In addition, the substrates used in Sufrin contained multiple catalytic sites, confounding the analysis. Moreover, Sufrin merely presents raw data without interpretive analysis. These data are not sufficient to lead one skilled in the art to consider DCMTase activity to be regulated via an allosteric site.

In contrast, Applicants have presented a thorough analysis with the type of data recognized in the art as demonstrating the presence of an allosteric site for modulation of DCMTase activity and ruling out active site inhibition and competitive inhibition (see Figures 12-19). Applicant has provided a thorough steady-state kinetic analysis using well-established mathematical models and three kinetic methodologies: initial velocity studies varying both substrates, dead-end inhibition and product inhibition. As discussed at page 53, lines 10-13, "DNA substrate inhibition was common to both small, single CpG containing DNA and large, multi-site DNA. A second nucleic acid binding region on the DCMTase, distinct from the active site, is implicated from both the substrate inhibition and the dead-end inhibition studies."

Applicants' claims require (a) inhibiting methylation of DNA comprising (b) contacting DCMTase with a synthetic inhibitor molecule (c) so as to form an enzyme/synthetic inhibitor molecule complex in the presence of DNA wherein (d) the inhibitor molecule comprises a C-5 methylcytosine molecule which (e) binds to an allosteric site on the DCMTase, which inhibits methyltransferase activity. The Patent Office has not shown that all of these elements are met by the cited reference. Sufrin fails to teach (a) inhibition (as it is understood by those skilled in the art), (c) formation of an enzyme/synthetic inhibitor complex in the presence of DNA, or (e) binding to an allosteric site on the DCMTase.

In addition to not teaching inhibition via binding to an allosteric site, the prior art does not teach or suggest, contacting the DCMTase enzyme with the synthetic inhibitor molecule in the

presence of DNA. Instead, Sufrin teaches substrates for the enzyme and compares the inherent activity of the different substrates. (See col. 4, lines 13-25, identifying the disclosed analogs as substrates that have the potential to be methylated by DNA methyltransferases.) Their "inhibition" is merely comparatively less activity when comparing one substrate to another. This is not the same as using an inhibitor molecule to inhibit the ability of the enzyme to methylate a DNA molecule.

Because the prior art, taken alone or in combination, fails to teach or suggest each element of Applicants' claims, Applicants respectfully request the rejection based on the prior art be withdrawn.

III. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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